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Application for Patent

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(בעברית) (Hebrew)
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(באנגלית) (English)
Methods and Apparatus for Stopping and/or Dissolving Acoustically Active Particles in Fluid

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Methods and Apparatus for Stopping and/or Dissolving Acoustically Active Particles in Fluid

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c:630/02782

Methods and apparatus for stopping and/or dissolving acoustically active particles in fluid.

ABSTRACT

Acoustically active particles in fluid pushed by ultrasonic radiation towards a surface in order to slow, stop and arrest them. If the Acoustically active particles consist of gas or gas wrapped in some kind of membrane (gas bubbles), further ultrasonic energy can be applied in order to shrink the bubble. Devices built based on this invention can be used, among the rest, to neutralize hazardous air bubbles during cardiovascular and cerebral invasive procedures, or to arrest accumulate, and make a controlled release of drugs encapsulated in membrane coated microbubbles in a targeted site at the body.

REFERNCES CITED

1. „Richard E. Clark, Microemboli during coronary artery bypass grafting: Genesis and effect on outcome" (J Thorac Cardiovasc Surg 1995;109:249-258).
2. „Neuropsychologic impairment after coronary bypass surgery: Effect of gaseous microemboli during perfusionist interventions", (Borger, Michael A,., J Thorac and Cardiovasc Surg 2001;121:743-749).
3. U.S patent number: 5,811,658 filed in April 29, 1997.
4. "The acoustic filter: An ultrasonic blood filter for the heart-lung machine." (Karl Q. Schwartz. J Thorac Cardiovasc Surg 1992; 104: 1647-53).
5. "Dissolution of Multicomponent Microbubbles in the Bloodstream" (Alexey Kabalnov et al. Ultrasound in Med. & Bio. 1998, 24: 739-749).
6. "Noninvasive pressure measurement using microbubble contrast agent and wavelet transforms" (A.Bouakaz, P.J.A Frinking, N. de Jong. IEEE Ultrasonics Symposium 1997, 2000).
7. "Enhancement of Sonodynamic Tissue Damage Production by Second-Harmonic superimposition: Theoretical Analysis of Its Mechanism" (S.I Umemura, K.I Kawabata and K. Sasaki. IEEE Transactions on ultrasonics, ferroelectrics and frequency control, vol. 43, no. 6. 1996).

FIELD OF THE INVENTION

This invention relates to the handling of acoustically active particles such as gas in fluid, and more specifically to a method and systems which uses ultrasound to selectively stop and dissolve acoustically active particles in a flowing fluid.

BACKGROUND OF THE INVENTION

Microbubbles and gas emboli can be introduced to fluid in a vessel by two mechanisms:

1. They can be administered to a fluid in a vessel from an outside source (for example: via injection), or as gas trapped in a container (or other type of vessels) is released inside the vessel containing the fluid.
2. Or they can be formed inside the fluid itself (intra-fluid, intra-vessel) due to pressure changes. Fast intensive injection, turbulent fluid flow (stream), changes in vessels diameter, fluid flowing speed, etc. can all cause pressure changes, which result in formation of microbubbles and gas emboli.

Described below are different fields where this invention's apparatus and methods can be used in order to selectively arrest and dissolve the gas in the fluid.

1. During different forms of medically and clinically invasive procedures such as open heart surgeries, minimally invasive stent placement procedures in the cardiac arteries, interventional radiology procedures involving contrast media injection to the cardiovascular system including the cerebral vasculature, and the aorta, at X-ray angiographies under fluoroscopy, at CT scans and MRI scans and during intensive IV (intra-venous).
2. The field of targeted drug delivery to organism, where specially designed drugs can be slowed, arrested, accumulated and dissolved at a target site.
3. Other medical and non-medical applications

Field 1: Two types of central nervous system (the brain) deficits may occur after the described invasive procedures and the introduction of air bubbles and microbubbles into the arterial blood vessels supplying the brain: first, focal deficits (stroke), secondly, diffuse cerebral dysfunction, encephalopathy and cognitive damage. Most often there are subtle mental damages, mild intellectual impairment, confusion or agitation, memory loss, personality changes or depression. When damage is severe, loss of consciousness may occur, coma and even death. The parameters which affect the extent of the brain damage due to the microbubbles are the e.g., bubbles individual size, the total air volume and the load (the volume of the bubbles at a given time period). Current techniques for stopping the formation and advancement of the microbubbles and air emboli conclude at changing the bubble oxygenators to membrane oxygenators at the bypass machines in heart surgery and using current barrier filter technology which is limited to relatively large filter pore sizes ranging from 33 to 40 μm. Pore sizes in the range of cerebral capillaries (7 μm) and red blood cells (8 μm) would probably improve the filtration of microbubbles but have a high resistance to flow and would induce more red blood cell trauma and is a potential source for contamination. Also due to the pressure changes near the filter, large bubbles condense in front of the filter, pass through its pores, exit again and advance towards the brain. Even when using modern bypass machines, studies including "Richard E. Clark, Microemboli during coronary artery bypass grafting: Genesis and effect on outcome" (J Thorac Cardiovasc Surg 1995;109:249-258), "Neuropsychologic impairment after coronary bypass surgery: Effect of gaseous microemboli during perfusionist interventions", (Borger, Michael A,., J Thorac and Cardiovasc Surg 2001;121:743-749) show, that bubbles are still present at vessels beyond the filter and at the brain,.

A U.S patent number: 5,811,658 filed in April 29, 1997 based on the article: "The acoustic filter: An ultrasonic blood filter for the heart-lung machine." (Karl Q. Schwartz. J Thorac Cardiovasc Surg 1992; 104: 1647-53), describes a new acoustic filter which can replace or be added to the mechanical filer. Ultrasonic energy is used to divert air bubbles from the main bloodstream to a different chamber where they can be removed. This type of filter can prevent only the bubbles formed at the oxygenator from reaching the blood vessel, but not the air bubbles formed at the aorta where the arterial line injects the oxygenated blood at high pressures, the emboli formed due to surgical intervention and air accumulated in the heart which account for most of the air emboli during valve replacement surgeries.

For systemic, cerebral and cardiac arterial catheterization it is recommended to extract slowly the contrast media saline from the bottle and inject it slowly to the patient. These procedures cannot be followed in the intense and dynamic nature of these interventional procedures. Even if the staff gives careful attention for the formation of bubbles, contrast media must be injected intensely in order to get good imaging of the vessels. Brain damage due to air emboli during IV is an uncommon condition. If a PFO (patent foramen ovale)

condition is diagnosed in a patient, the medical staff is encouraged to pay meticulous attention to the formation of air bubbles in intravenous catheters during operation and the procedures in the intensive care units (ICUs). PFO prevail in one out of four people and for most of them the shunt between the right and left atrium is silent. Although even for mild condition of PFO, increasing the right atrium pressure (for example by taking deep breath) results in passage of venous blood from the right atrium to the left side. Sources suggest that 2 to 3 ml of air passing through the PFO shunt is enough to cause serious brain damage and stroke.
Neither of the above-described prior art devices and techniques was able to effectively arrest and prevent the bubbles, both from outside source and intra-vessel, from reaching the brain. Further more no prior art described here could be fitted to almost any type of standard tube and stop and dissolve the bubbles before they enter the body and causing ischemia attacks on different organs of the body including the brain.

Field 2: This invention can be used to stop and dissolve microbubbles not only when they are harmful to the body but also where there is need to stop and accumulate them in a specific location in order to use their therapeutic effect.
Cancer is 2nd larger killer in the world. One in three Americans will eventually develop cancer. These patients are usually treated with surgery, drug therapy, and radiation therapy. Many patients are given a combination of therapies. Treatment with anticancer drugs may be given intravenously (injected into a vein) or by mouth. The drug travels through the bloodstream in order to reach cancer cells anywhere in the body. Chemotherapy can be used as the main treatment for the primary cancer or to those whose cancer have spread and metastasize outside the organ at the time it is diagnosed, or spreads after initial treatments. Neoadjuvant chemotherapy often shrinks the cancer so that surgery can remove cancers that would otherwise be too large for complete surgical removal. Chemotherapy is given in cycles, with each period of treatment followed by a recovery period. The total course of chemotherapy lasts three to six months depending on the regimens used. People having chemotherapy sometimes become discouraged about the length of time their treatment is taking or by the harmful side effects they are suffering from.
Fatigue is one of the most common side effects of radiation and chemotherapy.
Though it is not medically harmful, hair loss can be an upsetting side effect.
If hair loss does occur, it usually begins within two weeks from the start of therapy and gets worse 1-2 months after the start of therapy.
The side effects of chemotherapy depend on the type of drugs used, the amount given, and the length of treatment. Other side effects of chemotherapy treatment are: serious heart conditions, nausea and vomiting, loss of appetite, mouth sores, a higher risk of infection caused by a destruction of white blood cells, bruising or bleeding after minor cuts and shortness of breath. Very rarely, certain chemotherapy drugs may cause *acute myeloid leukemia* or AML, a life-threatening cancer of white blood cells years or decades after treatment. The reason of these side effects is the chemotherapy killing property which targets the mitosis mechanism of the cells. Despite the advances in cancer treatment, there are many areas where the need for effective chemotherapeutic agents remains significantly unmet: advanced prostate cancer, uterus cancer, liver and renal cancer, colon cancer, lung cancer, brain and breast cancer. A treatment for certain types of cancer is hormonal manipulation, which is a non-curative approach. Many patients undergo radiation and chemotherapy treatments. In forty five percent (45%) of newly diagnosed cancer patients and in ninety percent (90%) of patients receiving chemotherapy, cancers are resistant, to varying degrees, to the chemotherapy.

In order to develop site specific drugs which allow more precise targeted drug delivery to the tumor site, great efforts are being made, led by the industry giants: "Du-Pont" which recently acquired "Imarx"-microsphere technology leader and Johnson & Johnson with the acquisition of "Alsa"- developer of the DOXIL® and other lipid coated drugs, and also by several companies including "POINT-Bio medical" and "CAV-CON". These chemotherapy drugs are encapsulated in lipid (or other substances) microspheres (microbubbles) and can be coated with antigens to be more specific to the cancer cells receptors. The microspheres can be monitored via ultrasound device, and even a triggered explosion of the microsphere is possible once the chemotherapy has been absorbed by phagocytes within the tumor.
The invention in this patent can be used in order to enhance the effectiveness of encapsulated drugs and chemotherapy or other type of drugs (antibiotics, thrombolytic agents, etc.) by stopping, slowing, and accumulating the encapsulated drug in the target site. After the encapsulated drug uptake by the designated cells, the outer shell is rapidly dissolved, therefore releasing the encapsulated drug. This way the drugs undergo less systemic cycles and they have greater bioavailability in the targeted area. This results in fewer side effects, and increased intake possibility by the targeted cells. A special catheter can be used in order to release the drugs in the arteries supplying the targeted site, allowing even more accurate drug delivery.

Field 3: If acoustically active particles need to be stopped or dissolved in any situation, in flowing or arrested fluid in any kind of vessel (container, tube etc.) specific apparatus can be designed using the basic physical principle patented here as a method for stopping and dissolving acoustically active particles in fluid.

SUMMERY OF THE INVENTION

The present invention includes methods and apparatus for selectively slowing stopping arresting and/or dissolving acoustically active particles such as gas in fluid. Acoustic radiation, e.g. ultrasonic energy is used to push the particle in a moving fluid against a wall, or any kind of surface (flat, round, bumpy, etc.), where they are not able to advance with the flow due to friction and static pressures. Acoustically active particle can be consisted of gas or gas encapsulated in some kind of membrane (for example lipid coated microbubble or free microbubble). If it is subjected to acoustic radiation pressure, it can be pushed against a surface and then be subjected to rapid ultrasonic "hits" (or cycles) which cause the gas bubble to deform and break to ever-smaller gas bubbles. The smaller the gas bubble the faster it shrinks and the gas diffuses to the surrounding fluid. Almost similarly, the gas bubble can be pushed in a sufficient speed towards the surface where it passes rapid deformation (beacause it hits the surface) and as a result breaks and splits to smaller bubbles. Smaller bubbles shrink more quickly. The acoustic radiation (which is a form of wave) can be incorporated with, superimposed by, or be shaped in the stopping process (if needed) with a special wave pattern, e.g. waveform, which safely shrinks trapped gas bubbles through diffusion to the surrounding fluid, without causing cavitations and jet formation that results in shearing forces on the surface and may damage it. This specially tailored "shrinking" waveform can be applied before, during and after the stopping process or as independent process. The result is a contactless filtration of acoustic particles and gas bubbles, which can be introduced to the fluid both from outside source and intra- fluid, from the fluid.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1.1: Illustrates the velocity profile of fluid flowing inside a vessel (e.g. tube). X represents distance from the vessel wall. V axis represents flow velocity. R is the radius of the cylindrical vessel.

Fig 1.2: Illustrates the velocity profile of fluid flowing near a surface of arbitrary shape. X represents distance. V represents flow velocity.

Fig 1.3: Illustrates the "coin" effect. As the gas bubble 1 is pressed against a surface 2 by ultrasonic radiation pressure, the radii $<<\mathbb{R}$ at the surfaces of the "coin" lengthen, and the radii r at the edge of the "coin" shortens increasing the surface tension at the edges and accelerate the diffusion of gas long arrows from the bubble to the fluid.

Fig 1.4: Illustrates a macro gas bubble trapped against a flexible bottle wall , at three critical time points, as it breaks to smaller bubbles due to the force exerted on it by the hitting fingertip.

Fig 1.5: Illustrates the first case where the bubble breaks to smaller bubbles as it hits the surface due to the acoustic radiation forces exerted on the bubble.

Fig 1.6 illustrates a bubble which is already arrested against the surface in four time periods i-iv, as it is broken to smaller bubbles after each ultrasonic radiation pressure pulse.

Fig 1.7: Illustrates the asymmetric waveform which is the sum of the waves used in the first technique of clause VI. t represents time. A is the pressure amplitude.

Fig 2.x: In order to explain the principle theory of the present invention, an example illustration of acoustically active particle (in this case air microbubble) is used. The invention is in no way limited to the example presented. The ultrasonic radiation can be beamed from any direction relative to the surface and the direction of the fluid flow. The ultrasonic force, duty cycles and wavelengths used are not limited and will be applied according to required needs. The fluid and the particle viscosity coefficient, velocities (relative and absolute), specific mass, density and volumes are variable. Sizes used in the example are not limiting. Fig 2.0 is a legend for all of Fig 2.x: 1 is the acoustic particle (more specific air bubble). 2 is the speed vector of the fluid (and the suspended particle). 3 is an arrows Non parallel to Vz, it describes diffusion of gas molecules from the bubble to the fluid. 4 is a dot Illustrates gas molecule diffused to the fluid. 5 is acoustic radiation pressure waves, (ultrasound energy) the field move to the direction of the arc's head (in this case directly down). 6 is the direction of the particle motion. 7 is Ultrasonic Head which produces acoustic pressure waves. 8 is surface (or vessel wall).

Fig 3.x: Nonimaging transducer or transducers array with stopping and dissolving capabilities; plus two monitoring ultrasound transducers before and after the stopping and dissolving transducer/array. This example is of a device that can be used for the filtration of blood from microbubbles and particles at the hart-lung machine, and on the patient neck during open-heart surgeries and other invasive procedures to prevent the harmful microemboli from reaching the brain.

Fig 4.1: Apparatus for stopping and dissolving acoustically active particles suspended in flowing fluid in a tube 2. The apparatus consist of a piezo-electric transducer 1 which emits

ultrasonic radiation in a special pulsating regime. In more advanced embodiment of the apparatus bubbles detectors and superimposition techniques can be used.

Fig 5.1: Focused transducer or transducers array with stopping and dissolving capabilities. This device can be used for stopping encapsulated drugs at a specific (e.g. tumor), thus enhancing the effectiveness of the drug, and reducing the systemic circulation of the drug, that results in reduced side effects.

Photo 1: Shows a 1.5 liter soda bottle with an air bubble arrested against its wall.

Photo 2: Shows the several small bubbles that broke from the single bubble arrested against the bottle wall, after the bottle wall was rapidly hit several times at the area where the single air bubble was arrested by a plastic pen.

DETAILED DESCRIPTION OF THE INVENTION

The principle method of the invention is application of acoustic radiation force to slow, or stop, or shrink in the same process or apart, acoustically active particles suspended in fluid.

I. By exposing acoustically active particles suspended in a fluid to ultrasonic field traveling through fluid medium, the particles are pushed in the direction of the ultrasonic field propagation. A surface is placed in the path of the ultrasonic waves field propagating in the fluid. The acoustic radiation force exerted on the acoustically active particles when they enter the ultrasonic field pushes the particles towards the surface and against it. Because acoustically active particle substantially differ acoustically from their fluid environment, they are most affected by the ultrasonic energy, and selectively pushed by the ultrasonic energy while the pushing effect on the rest of the fluid due to the ultrasonic field is negligible.

II. The velocity profile of fluid in a cylindrical vessel is usually of parabolic shape (as described in Fig 1.1) because of increased friction forces near the wall surface, reaching maximum value at the center of the vessel and gradually approaches to zero at the vessel wall.
This parabolic shaped velocity profile is true for fluid flowing in the vicinity of Geometric form affixed (or advance slower relative to the flow of the fluid) in the flowing fluid gradually increasing its value as the distance from the form is increased Fig 1.2. (shorter distance between a fluid particle and the surface, means slower particle speed).

III. The friction forces between two materials (particles, surfaces, particles and surfaces, etc.) are in direct relation to the magnitude of the force (e.g., acoustic radiation force) pushing them against each other (e.g., the particle against the surface).

IV. (1) the pushing property by ultrasound energy (e.g., ultrasonic radiation force) of acoustically active particles through the flowing fluid (clause I), (2) the low velocity of the fluid flowing near a surface (until a negligible speed close to the surface itself) due to frictional forces between the fluid particles and the surface (clause II) (3) and the friction forces between the acoustically active particles and the surface as they pushed against each other by the ultrasonic radiation force (clause III), are combined together in this invention method in order to selectively slow, stop and confine acoustically active particles in a fluid, by pushing them against a surface. These three individually physical properties are utilized in the subsequent manner: Exposing acoustically active particles suspended in a fluid (the fluid

flowing speed can be zero or greater to all directions) to ultrasonic field of waves traveling in the fluid medium. The said particles are pushed in the direction of the ultrasonic field propagation because of acoustic radiation force exerted on the acoustically active particles. A surface is placed (the wall of vessel containing the fluid can be used) in the path of the ultrasonic field propagation in the fluid, or the ultrasonic waves can be aimed towards the surface. As the acoustically active particles are pushed closer to the surface (clause I), they pass through a decreasing flowing speed of the fluid (clause II), therefore their own speed (if the acoustically active particle has no self propulsion, being suspended in the fluid) is decreasing too. The acoustically active particles reach the surface and are pushed against it by the acoustic radiation force. This creates frictional forces between the surface and the acoustically active particles preventing their movement (clause III).

Fig 2.1 This Illustration relates to clause V. i. In t=0 the gas bubble is pushed against the surface where the friction forces prevent its movement. ii. Next, the bubble is pushed against the surface and condenses because of the excess arterial pressure and the ultrasonic field. iii - iiii. The bubble shrink and the gas molecules diffuse to the surrounding fluid medium. iv. All the gas diffused to the fluid, dissolve in it and the bubble has been neutralized.

V.a Acoustically active particles in a fluid can contain or consist of gas (for example: air microbubbles, lipid coated microbubbles, and types of ultrasonic contrast agents). As discussed and explained in the article: "Dissolution of Multicomponent Microbubbles in the Bloodstream" (Alexey Kabalnov et al. Ultrasound in Med. & Bio. 1998, 24: 739-749), according to the kinetics of the dissolution process for bubbles in a liquid based on Epstein and plesset equation, gas bubbles naturally shrink as a result of the surrounding pressure. The above method (clause IV) can also include shrinking the particles by subjecting the particles to the surrounding fluid overpressure (for example excess arterial pressure) e.g. increased fluid static pressure closer to the surface, by ultrasonically pushing the particles toward a surface and against it. Further more, according to the article: "Noninvasive pressure measurement using microbubble contrast agent and wavelet transforms" (A.Bouakaz, P.J.A Frinking, N. de Jong. IEEE Ultrasonics Symposium 1997, 2000) and Epstein and Plesset Equations the radiation pressure exerted on the bubble by the ultrasonic radiation pressure will press it against the vessel wall (clause IV). This will result in changing the bubble shape from a sphere to a large thin coin. The large surface tension at the edges of the "coin" will accelerate gas difusion into the fluid (as described in Fig 1.3). It can be easily shown that for a large enough "coin", the required radion pressures are less than 0.5 mmHg.

V.b. As explained in the sources mentioned in clause V.a, the gas bubbles shrink faster as their radii decreases (the smaller the bubble, the faster it shrinks). For example, air bubble with a radius of 2.5μm in the bloodstream will dissolve to the surrounding fluid in about 0.17sec. While a bubble with a radius of 10μm will dissolve in around 5sec. By exerting abrupt pressure changes onto a bubble, it deforms, and splits (breaks) into smaller bubbles. This phenomenon can be easily demonstrated by trapping a macrobubble (e.g. can be seen with a naked eye) against a flexible vessel wall and snapping a finger on the flexible surface (for example the exterior of a standard 1.5 liter bottle containing soft soda or water). Fig 1.4 illustrates a macro gas bubble 1 trapped against a flexible bottle wall 2, at three critical time points. In t=0, i the fingertip 3 is advancing towards the bottle wall and the bubble. Moment later ii the fingertip hits the bottle wall and immediately retreats iii. This "whiplash" strike exerts shearing forces on the bubble, breaking it to smaller bubbles 4 and can be repeated until the bubbles reach a critical size and dissolve completely to the surrounding fluid. Photo 1 and Photo 2 shows the before and after state (respectively) of an air bubble arrested against a bubble wall after it was hit several times by a plastic pen. The same principle applied on gas bubbles in a vessel using ultrasonic energy. The bubble is deformed and breaks to

smaller particles first, when it pushed towards the surface and shattered against it (when the ultrasonic power and bubble momentum are sufficient). Secondly, when the bubbles arrested against the wall, a regime of pulsating ultrasonic energy hits the bubbles and breaks them to ever-smaller bubbles, which shrink faster and dissolve to the surrounding fluid. Fig 1.5 illustrates the first case where the bubble breaks to smaller bubbles as it hits the surface due to the acoustic radiation forces exerted on the bubble. Fig 1.6 illustrates a bubble which is already arrested against the surface in four time periods i-iv, as it being break to smaller bubbles after each ultrasonic radiation pressure pulse.

VI. The above method (clause IV, V) can further consist of two techniques for stimulated shrinking gas bubbles. Both of them consist of a unique ultrasonic temporal waveform and, which is employed in order to shrink the gas filled or gas consisted particles faster and more affectively. The ultrasonic waveform can be generated by the same ultrasonic transducer used for the above method (clause I-V), or by a separate acoustic source (for example different pieso-electric crystal) congruent to the above method ultrasonic field, or aimed at its interaction area with the surface and/or the particles.
The first shrinking technique relays on principle discussed in the article "Enhancement of Sonodynamic Tissue Damage Production by Second-Harmonic superimposition: Theoretical Analysis of Its Mechanism" (S.I Umemura, K.I Kawabata and K. Sasaki. IEEE Transactions on ultrasonics, ferroelectrics and frequency control, vol. 43, no. 6. 1996) which shows, that expanding gas bubbles by rectified diffusion using relatively low harmonic ultrasound frequencies (about 0.5 MHz and 1 MHz) and inducing asymmetric oscillation of bubble pressure with relatively sharp valleys and broad peaks, is feasible. In this invention the presented principle is implemented in different way, by superimposition of relatively high harmonic ultrasound frequencies (for example about 5Mhz and 10Mhz) and inducing asymmetric oscillation of bubble pressure with relatively sharp peaks and broad valleys (the principle waveform described in Fig 1.7. This is done in order to accomplish optimal bubbles compression and diffusion of the gas from inside the bubbles to the surrounding medium safely and without causing cavitations and jet formation that can be harmful to the surface. The pattern of acoustic waves (waveform) can be applied during all or part of the described process, to safely diffuse the gas from the bubble to the surrounding fluid without causing cavitations and jet formation that can be harmful to the surface.
The second technique for shrinking the gas bubbles, is by superimposing low intensity, low frequency ultrasonic wave (or waves), at about the resonance frequency of the bubbles. This is done in order to impose on the bubbles stable cavitations of low amplitude. As the bubbles are pressed against the surface by the main relatively high intensity, high frequency ultrasonic filed, asymmetric pressure surrounds the bubbles (from the surface, and the fluid). This causes asymmetric bubbles oscillations which fragmentize larger bubbles into smaller bubbles, the smaller the bubble the faster it shrinks and diffuses to the surrounding medium (according to Epstein and plesset equation). The cavitations induced by this technique are nonviolent and subtle, in order not to causes excessive sheering pressure on the surface, violent bubble collapse and jet formation.

VII. The ultrasonic field (clause I-VI), generated from the acoustic source or sources, can be further focused to a specific volume or point (e.g. site) in the medium in order to increase the acoustic radiation forces in the said site.

VIII. The above ultrasonic field (clause I-IV) can be applied in a continuous state, or can be generated on command by human operator or electronic device. The ultrasonic field can be generated after detection of the acoustically active particles by special ultrasound transducer

using the Doppler principle as is well known to does who are familiar in the art of ultrasound or any other detection method, depending on the use, conditions and needs.

IX. The ultrasonic field intensities, duty cycles, frequencies and acoustic properties, and the number of acoustic sources, their shape, dimensions, placement and acoustic properties, can be fitted and maximized in order to accomplish the best results (of the method) for a given need, use and environment parameters, according to the basic principles (represented by clauses I-VIII) set forth in this patent method.

Ultrasonic waves at frequencies much greater than the resonant frequencies of the acoustic active particles can be used in the method in order to avoid cavitations and jet formation that can damage the fluid or surface (in case of air microbubbles frequencies in the range of about 4 MHz and above can be used). Except for the low intensity, low frequency ultrasonic wave used in the second technique in clause VI.)

Clauses I-IV describes the slowing, stopping and arresting mechanism by method of this invention. Other factors, laws of nature, and forces can participate in the described method improving or worsening its effect. Yet as long as the basic elements of the invention are provided (acoustic radiation pressure from acoustic source or sources, fluid, acoustically active particle and surface), the method of this invention is always the principle or only effect that slows stops and arrest the acoustically active particles.

In order to describe, in the best clear and simple way, the invention method for using ultrasonic energy to slow, stop, arrest and dissolve acoustically active particles, a typical representative situation is described. Bubble suspended in fluid, flowing through a straight round tube when it enters an ultrasonic traveling waves field perpendicular to the flowing direction. The bubble is then pushed by the field towards the wall, and slows, until arrested against the tube wall. Making projections from the set of the following equations and explanations for other types of situations where there is need to filter, slow, or stop and arrest, or dissolve acoustically active particles in fluid, are intuitive and do not involve any kind of inventive skills. Providing the basic elements of the invention: acoustic radiation source, fluid, acoustically active particle and surface, in a rationalistic and skillful way according to the principles described in this invention, enables to slow, or stop and arrest, or dissolve acoustically active particles in a fluid. Refinements to the different elements parameters, in order to accomplish a better slowing, or stopping, or dissolving of acoustically active particles in a fluid in a given environment and element conditions, require no more than understanding the invention methods and the process of trial and error.

Fig. 2.2 illustrates an acoustically active particle (in this case spherically shaped) suspended in a fluid. Spherical gas-filled bubbles have radically different acoustic properties and have much lower mass than biconcave fluid-filled (nonresonant) red blood cells or other irregularly shaped fluid-filled cellular blood elements, therefore the bubbles are preferentially affected by the acoustic radiation force. Acoustic radiation force refers to the force exerted on acoustically active particles (such as microbubbles and plaque) suspended (or moving) in fluid when exposed to a field of traveling ultrasound waves. Ultrasound (e.g. ultrasonic energy) can be produced by a single-element ultrasound transducer. Only traveling waves produce the needed acoustic force to push suspended particles and bubbles. Standing waves would cause particles to collect at the acoustic pressure nodes or maxima. Acoustic radiation force is a second-order or nonlinear effect, which is related to the B/A of the system. (The term B/A refers to the coefficients A and B that describe the first two

components of the acoustic pressure equation. As a sound wave travels through a medium and passes a given point, the density of the medium increases and then decreases as each peak and trough of the sound wave passes that point. Acoustic pressure at any point is therefore related to the relative change in density of the medium (Δdensitiy). The relationship is represented as a Taylor expansion:

$$\Delta\text{Pressure} = \sum(A(\Delta\text{densitiy}) + B(\Delta\text{densitiy})^2 + C(\Delta\text{densitiy})^3 + \ldots)$$

Fig 2.2: The black dot represents an acoustically active particle (the bubble). The horizontal line represents a surface, e.g., wall. Vz is speed vector of the fluid and suspended bubble.

It may therefore be seen that B/A is a measure of the degree to which the pressure-density relationship deviates from linear. The nonlinear components (B, C, etc.) become important when the sound is loud (i.e., A). For microbubbles in water (or blood) the B/A is on the order of 1000). Microbubbles are an example for very acoustically active particles. At ultrasound frequencies near the resonance frequency of the bubble, the scattering cross-sectional area increase by several orders of magnitude above the geometric cross section. The larger the scattering cross-section, the more acoustic radiation force will be exerted on the bubble. The strength of the acoustic force depends on the ultrasound direction, frequency and signal strength, and the size, mass and acoustic qualities of the object to be filtered. Objects that are acoustically different from the surrounding medium are the most affected by the ultrasonic energy.

Fig 2.4 In the example, the ultrasonic radiation force applied on the particle is F and the mass of the particle is m. because of the viscosity, friction force is also exerted on the particle in the opposite direction: Fvis.

(1) $$F_{vis} = 6\pi r v \eta$$

When: r- the particle radius
v- the particle velocity
η- viscosity coefficient

The equation of motion is:

(2) $$m\frac{dv}{dt} = F - F_{vis} = F - KV$$

Where: $K=6\pi r\eta$

In case the particle is a bubble ρ is the gas density. (for air $\approx$1000 Kg/m^3).

(3) $$m = \rho \cdot \frac{4\pi}{3} r^3$$

The solution of the equation:

(4) $$V(t) = \frac{F}{K}\left[1 - e^{-\frac{t}{\tau}}\right]$$

When: $\tau = \frac{m}{K}$

(5) $$\tau=\frac{m}{K}=\frac{\rho\cdot\frac{4}{3}\pi r^3}{6\pi r\eta}=\frac{2}{9}\rho\frac{r^2}{\eta}$$

In order to simplify the equation. If the particle is in the order of microns (e.g. microbubble) it can be assumed that the bubble reaching its limit speeds in a negligible time (for example around 40μsec for a 20μm diameter air bubble.)

(6) Therefore: $$v=\frac{F}{K}$$

The acoustic radiation pressure (Prad[N/m^2]) is calculated from the ultrasonic power for surface unit (Warea[W/cm^2]), divided by the speed of sound in the medium (C[cm/s]). If the application of said acoustic pressures is on biological systems, than according to Dewy and Sparto "thermal dose equation" and the "bio-heat equation", and taking into account the very effective heat perfusion to a rapidly streaming blood, it is allowed to apply radiation power/output of 100 – 200 w/cm^2 for certain periods of time without causing excessive heating.
The force upon the particle will be the radiation pressure (Prad) multiplied by the Geometric cross section (the surface facing the radiation direction of propagation).
In case of a spheric particle (e.g. microbubble) the acoustic force will be:

(7) $$F_{rad}=P_{rad}\cdot\pi r^2$$

The limit speed of the particle towards the surface is:

(8) $$v=\frac{F}{K}=\frac{P_{rad}\cdot\pi r^2}{6\pi r\eta}=\frac{Prad\cdot r}{6\eta}$$

Therefore the time it takes for the particle to pass a distance R to reach the surface is:

(9) $$t=\frac{6R\cdot\eta}{P_{rad}\cdot r}$$

If for simplicity (as in this example illustration), the particle is suspended in a fluid medium which move perpendicular to both the radiation force and the surface, and the surface is flat (both the radiation force and the surface do not have to be perpendicular to fluid flow, and the surface do not have to be flat); than the propagation profile of the particle upstream is according to Bernouli's equation The flowing of the fluid and the particle is decelerating closer to the surface, until a complete arrest of the particle as a result of increased friction forces is achieved.

Fig 2.5: In the illustration above Vz is the flowing vector. ΔZ is the distance the bubble passes parallel to the surface, until the bubble reaches the surface. R is the distance from the bubble initial position (before application of ultrasonic force) and the wall.

(10) The flowing profile: $$v_z(x)=v_z(o)\left[1-(\frac{x}{R})^2\right]=v_z(o)\left[1-\frac{v^2t^2}{R^2}\right]$$

While approaching to the surface the particle will travel upstream a distance of:

$$\Delta Z = \mathcal{V}_z(0)\int_0^{R/\mathcal{V}}\left(1-(\frac{\mathcal{V}t}{R})^2\right)dt = \mathcal{V}_z(0)\left[\frac{R}{\mathcal{V}}-\frac{1}{3}\frac{R}{\mathcal{V}}\right]$$

(11) $$\Delta Z = \frac{2}{3}\mathcal{V}_z(0)\cdot\frac{R}{\mathcal{V}}$$

The surface (biological, inorganic materials, etc.), particles (gas filled, fluids filled, etc., of any geometry) and environmental proprieties (biological, heat doses, flowing velocity, etc.) are considered when choosing the ultrasonic wave properties to be used.
For gas bubbles, the stopping method can be accompanied by the dissolving method (clause V,VI) or both of them may be applied on their own, depending on needs. The ultrasonic waveform applied to the bubble is modulated in order to diffuse the gas from inside the bubble to the fluid medium without causing the bubble to collapse abruptly and form a jet, or creating high shear stresses because of extreme oscillations of the bubble that may damage the surface (e.g. the vessel wall). The ultrasonic frequencies used are about 1 MHz and above, preferably Between 5 MHz and 10 MHz.

The apparatus and methods for selectively stopping and dissolving gas in moving fluids described in this patent, is in no way confined to the examples from the medical world described here and they can be implemented to different areas as well.

The BubbleBuster- apparatus and method for stopping and dissolving air bubbles at the common carotid arteries and refers specifically to field one of this invention's "Background of The invention".

Fig 3.1 Illustration of a principal embodiment of the ultrasonic head of the **BbubbleBuster-** apparatus and method for stopping and dissolving air bubbles at the common carotids. The Ultrasound Head consist of two "Doppler" elements **1,** the main ultrasound transducer **2** and expansion slot to allow attach more transducers for better arrest and dissolve capabilities **3.** The length of the head is about 5cm or shorter, to fit an average human length of the common carotid. Pediatric version of the invention should be shorter. The ultrasonic head consists of 3 basic elements (which can be combined into one element or any number of elements) in a sequence.
The first element is an acoustic source (e.g., piezo-electric transducer) capable of detecting blood flow in the carotid artery (by analyzing the Doppler Effect), and to distinguish between blood free of acoustically active particles (to be exact air bubbles, microbubbles) and the presence of bubbles in the blood. Products with these properties are commercially available.
The second element is the acoustic source described for the principal method of this invention presented at clauses I-IX. The design of the acoustic source is maximized, according to ultrasound physics basic laws, in order to accomplish the best results for safely and selectively stopping and shrinking the bubble. The bubble is pushed against a surface (clause II), in this method and apparatus the surface used is the blood vessel wall. The pushing and shrinking process is accompanied by the shrinking waveform described in clause VI.
The third element has the same acoustic source properties as the first element. It detects blood flow, and air bubbles (acoustically active particles) in the blood. If bubbles manage to

pass the second element, the third element detects them and alerts the user, and/or changes the second element acoustic output via feedback mechanism.
Air bubbles suspended in the bloodstream which passes through the carotids, are detected by the first element, selectively and safely neutralized (stopped and shrunk) by the second element and the third element provides confirmation that the bubbles detected by the first element have been neutralized by the second and provides feedback to the second element.
The first and third elements in the ultrasonic head are also used to detect the carotid artery by sensing the blood flow through it. By comparing intensities of both elements, alignment of the ultrasonic head long axis with the carotid flow direction can be achieved.

In a preferred embodiment of the apparatus, the first and third elements inputs are connected to the second element output, in order to apply a suitable ultrasound output for pushing the bubbles to the wall within the ultrasound waves field, and to apply the exact waveform for shrinking the bubbles, for the changing bloodstream, bubbles diameter, bubble volume, etc. The first and third elements also connected to each other in order to enable alignment of the head long axis and the carotid bloodstream direction. Fig 3.2 is an illustration describing possible communication connections between the three elements electronic cards, controlled by computer software.

Fig 3.3 Illustrates a possible instrument design (preferred embodiment) for the apparatus, with two ultrasonic heads 1 for both carotids 2, which are placed on the neck 3. The view is a cross-section as the patient lying on his back. The Ultrasonic Heads are situated on levers 4 which allow freedom of movement at all axis for the Ultrasonic Heads to allow easy adjustment and alignment of the Ultrasonic Heads elements along the carotids. The patient neck is placed on special designed inflatable head and neck pillow 5 (made from foam or sponge, etc.), in order to prevent acute changes of the patient head and neck position. The base of the apparatus 6 can contain the electronics for the device, or the electronics can be placed in another box. Other instruments (monitor, user interface, etc.) should be placed in the most convenient manner.

Fig 3.4 illustrates a 3D embodiment of Fig 3.3 cross section (artist impression). The numbers in the two illustrations correlate. Two Ultrasonics Heads 1 for both common carotids 2 (illustrated by broken lines). The Ultrasonic Heads are situated on levers 4 which allow freedom of movement at all axis for the Ultrasonic Heads to allow easy adjustment and alignment of the Ultrasonic Heads elements along the carotids. The patient neck is placed on special designed inflatable head and neck pillow 5 (made from foam or sponge, etc.), in order to prevent acute changes of the patient head and neck position. The base of the apparatus 6 can contain the electronics for the device, or the electronics can be placed in another box. Other instruments (monitor, user interface, etc.) should be placed in the most convenient manner. The two black circles illustrated on the face of the left Ultrasonic Head 1, represent the "Doppler" elements, and the X enclosed in the circle represent the main ultrasound transducer (or transducers). Other instruments (monitor, user interface, etc.) should be placed in the most convenient manner.

Fig 3.5 illustrates a cross-section of a vessel 1 (for example a blood vessel). Acoustically active particles (for example gas bubbles) suspended in fluid 2 flowing inside the vessel are being pushed (black arrows) toward the vessel wall by ultrasound waves field 3 focused onto the vessel. The ultrasound waves propagate in the general direction of the white arrow 4. The two black arches 5 illustrate the ultrasound field limit as it being focused at the vessel

(the focus can include the vessel and the surrounding, all the vessel or part of it, the focus site (point or volume) is not limited to a specific forms and sizes, and is determined by the acoustic source (or sources) properties in order archive the best results (stopping and dissolving capabilities) for given conditions.

Fig 3.6 illustrates the effect of the ultrasound field on gas bubbles (e.g. air bubbles) moving in a vessel (for example the carotid). The black arrows 1 illustrate the speed vectors of the fluid flowing in the vessel (faster flowing speed towards the middle). Bubbles 2 traveling through the vessel (the white arrow show the general flowing direction) detected by a "Doppler" acoustic source 3 capable of detecting acoustically active particles in a medium by applying and analyzing ultrasound energy 4 (also can detect flowing fluid, like blood flowing in the carotid). After the bubbles have been detected by the "Doppler" source, the main acoustic source 5 is activated creating acoustic radiation pressure 6, the ultrasound waves propagate in the general direction of the white arrow 6, The black arches 7 illustrates the lengthwise limits of the ultrasound waves field as it being focused. As the bubbles enter the waves field acoustic force is exerted on them 8, pushing them towards the vessel's wall. The bubbles continue their advancement in the flowing fluid (e.g. blood) slowing down because of increased friction closer to the wall, until they stop 9. Because of the acoustic radiation pressure, and because of the wave form being superimposed on the waves field, the bubbles pushed against the surface and the gas from inside the bubbles passes to the medium by rectified diffusion, thus shrinking and eliminating the bubbles 10. Since the surrounding fluid continue to flow, the bubble. Another "Doppler" source 11 monitor the vessel for remaining bubbles and provides a feedback loop for the system (can change the main acoustic source parameters in order to achieve better arrest and shrink capabilities).

The apparatus also includes a specially designed inflatable head and neck pillow (made from foam or sponge, etc.), in order to prevent acute changes of the patient head and neck position during the procedure.

The apparatus prevents dangerous air bubbles from reaching the brain through the carotids and causing brain damage as described in the background of this patent.
This is the general concept of the apparatus. More features, better acoustic elements, software, ultrasound imaging capabilities, etc. when added to this invention apparatus are all embodiment of the same apparatus which provides the ultrasound energy used in this invention method, and are not standalone inventions.
The apparatus preferable name is the BubbleBuster (or ultrasonic BubbleBuster).

The BubbleBuster In-line apparatus and method for stopping and dissolving air bubbles in arterial and venous lines and refers specifically to field one of this invention's "Background of The invention".

This apparatus and method is a simplified version of the BubbleBuster apparatus and method. The apparatus consist of a single "pushing" acoustic element (e.g. piezo-electric transducer). The acoustic element creates acoustic radiation pressure field as described in clauses I-IX. The element applying the acoustic energy is turned on and off in a special cycle regiment, in order to accomplish the best arresting and dissolving capabilities for a specific line (for example cardiopulmonary machine's arterial lines, contrast media catheters, high-flow venous lines, etc.). The bubbles are pushed towards the vessel wall by the pulsating

high frequency ultrasonic energy field, the bubbles may only stop at the vessel wall or they can already break and split to smaller bubbles if they hit the vessel wall with sufficient momentum. The acoustic element keeps pulsating, in order to break the bubbles arrested against the vessel wall to smaller and smaller bubbles as described in clause V.b. Smaller bubbles shrink and dissolve faster than bigger bubbles.
Fig 4.1 Illustrates a preferred embodiment of the apparatus which is basically a piezo-electric transducer 1 which is attached (clipped, glued, threaded, etc.) to a hollow tube (e.g. the line) containing fluid flowing in it 2. A preferred ultrasonic cycling regime can consist of: an ultrasonic energy pulse for the time it takes an average bubble to reach the vessel wall in sufficient momentum in order for it to deform and split (break) to smaller bubbles due to shearing forces on the bubble, and then about one cycles of rest. For example, it takes about 20msec for a bubble with a radius of 10μm reach the wall of a vessel 0.8mm in diameter, if ultrasonic energy of about 100w/cm^2 is applied, so a cycle regime of a 20msec ultrasound pulse and 20msec of rest can be used (1:1 relationship).
The apparatus can also incorporate bubble detectors (ultrasonic, optic etc.), and superimposition mechanisms as described in clause VI. and can be focused, and adjusted to best fit given needs.
The apparatus prevents dangerous particles and air bubbles from entering the body blood circulation and reaching vital organs in the body, where they can cause ischemia and damage to the organ.
The apparatus preferable name is the BubbleBuster in-line (or ultrasonic BubbleBuster in-line).

TheraSite - apparatus and method for slowing, stopping and accumulating encapsulated drugs in a specific site blood vessels and refers specifically to field one of this invention's "Background of The invention".

Fig 5.1 Illustrates the concept of the method and apparatus for selectively slowing down, stopping, arresting accumulating and dissolving, acoustically active particles (microbubbles) carrying encapsulated drugs, in a specific selected site.
i. Diagram representing possible blood vessel direction relative to the direction o the ultrasonic field direction. ii. Drugs encapsulated in microbubbles. iii. Blood vessel supplying blood to the targeted area (passes through the conjugated ultrasound waves but not through their focus. iv. Blood flow direction inside the blood vessel. v. The acoustic radiation pressure waves traveling through the ultrasonic field. vi. The ultrasound waves direction from one or multiple acoustic sources. vii. The acoustic source composed of single acoustic element or array of acoustic elements.
The principle used for this apparatus and method is the principle method described and explained in this invention (I-VI). The acoustic waves in this apparatus are focused (longitudinal and axial) to a designated site (volume) as mentioned in clause VII. In the focal volume the radiation pressure effect maximum. The effect decreases poterior and anterior to the focus volume. The decrease in pressure in a given area is proportional to the distance of the area from the focus (posterior and anterior), the f number (#f- the relationship between the acoustic source diameter and the distance from it to the focus), the ultrasonic wavelength and the acoustic properties of the medium.
In the focal zone (for example cancer tumor) the blood flows in different directions inside blood vessels (not necessarily perpendicular to the ultrasound waves field traveling direction). As a result, depending on the relative angle between the bloodstream and the ultrasonic field propagation, only part of the acoustic radiation force pushes the bubbles towards the vessel wall, causing it to stop. Example of extreme state: if the blood flow

direction in a vessel in the focal zone is parallel to the waves propagation, the waves will not push the bubble towards the wall, but will accelerate it away from the source in the flow direction.

A preferred embodiment of the apparatus consists of one or more ultrasound heads with one or more ultrasonic sources (or arrays). In order to allow accurate focusing by the operator, ultrasonic imaging capability can be added, or outside imaging instrument (MRI, C-arm, etc.) can be used in order to accurately find the site to be targeted, and focus the ultrasonic waves on it.

The advantages over regular systemic drugs (for example chemotherapy), is that the drug is physically stopped and accumulated at the targeted site, and because the drug is encapsulated in very acoustically active microbubbles, by means of ultrasonic imaging, the operator gets precise indication on the amount of drugs in the targeted site. When the operator (the physician) decides that the uptake process of the encapsulated drugs by the targeted cells is complete, he can then use the shrinking method (clause VI) in order to quickly diffuse the content of the microbubbles and with it the encapsulated drugs. Special ligands and vectors can be incorporated on the microbubbles membrane to allow grater specificity to targeted cells.

More features, better acoustic elements, focusing energy from several different direction, software, ultrasound imaging capabilities, etc. when added to this invention apparatus are all embodiments of the same apparatus which provide the ultrasonic energy used in this invention method, and are not stand alone inventions.

In order to further reduce the systemic spreading of the drugs a unique catheter is used to release the drugs into the artery (or arteries) which leads straight to the targeted site, thus preventing the systemic circulation of the drug until it independently reaches the ultrasonically targeted site.

The apparatus preferable name is the TheraSite (or ultrasonic TheraSite).

Conculsion:

In conclusion this invention provides a new method and apparatus for slowing, stopping and dissolving acoustically active particles in fluid using ultrasound energy in a unique way. The possibilities for improving the three different basic components of the invention, the acoustic wave source, the acoustically active particles and the surface shape (when the stopping surface is designed and added by the user and not a predetermined component like blood vessel wall) are countless. Two principal method and apparatus (slowing and arresting; diffusion of gas bubbles) as well as two principle embodiment of the invention where described in details.

We Claim:

1. A method to slow, and/or stop, and/or shrink acoustically active particles suspended in fluid by applying acoustic radiation force on the particle as described in the detailed description of the invention. comprising:
   a. Appling acoustic radiation pressure from an acoustic source or sources on acoustically active particle or particles suspended or moving in fluid.

b. Any kind of fluid/fluid, which is contained in any type of vessel, container, hose, open or closed, made from any kind of material (for example biological, metal, glass) flowing in any direction at any speed.

c. Acoustically active particles, or particles, which are acoustically different from the surrounding fluid medium, and are suspended or moving in any direction inside the fluid.

d. Creating a pushing force on the acoustically active particles by the acoustic radiation pressure. This moves them towards a surface and pushing them against the surface. The speed of the fluid and the particle (if suspended in the fluid) is reduced closer to the surface because of friction and pressure forces, reaching near zero movement at the surface.

e. The surface is made from any material (biological, and non-biological) and in any shape. The surface can be the wall of the vessel or container, and can be put in any direction relative to the flowing fluid, the acoustically active particles movement direction and the direction in which the acoustic radiation wave advances.

2. The composition of claim 1, wherein said steps, further include the step of applying acoustic pressure in order to press the acoustically active particle against the surface, preventing its movement.

3. The composition of claim 1, wherein the acoustic radiation pressure is changed according to the speed of the particles and the speed of the fluid, in order to slow, stop, the particles within the ultrasound beam range and limits (by pushing it against the wall).

4. The method of claim 3 where in the acoustic radiation power/intensity is applied on the particle in order for it to reach the surface and stop within designated range.

5. The method of claim 1, wherein the said particles are gas bubbles.

6. The method of claim 3, wherein the acoustic radiation pressure is further applied in order to shrink the bubbles, and diffuse the gas from which the bubbles consist, to the surrounding medium.

7. The composition of claims 1 and 3, wherein the principal ultrasonic wave is incorporated (superimposed) with one or more wave, in order to shrink the gas bubbles more effectively. The incorporation method described in clause VI of this invention Detailed Description of The Invention.

8. The method of claim 1 and 3, wherein the acoustic radiation is applied in pulses and sufficient energy in order to create shearing forces and stress on the bubble as it being hit against a surface by the ultrasonic filed, causing the bubble to deform and break into smaller bubbles.

9. The method of claim 8, wherein the acoustic radiation pulsing regime is further applied until the bubbles are small enough to rapidly dissolve to the surrounding fluid.

10. The method of claim 1, wherein the said particles are membrane coated gas bubbles (for example, Levovists®, Optisons®, LCMs- lipid coated microbubbles), which can also carry drugs.

11. The method of claim 3, wherein the acoustic radiation pressure is further applied in order to shrink the membrane coated gas bubbles, and diffuse the gas from which the bubbles consist to the surrounding medium.

12. The composition of claim 1 wherein the acoustic radiation wave e.g., ultrasonic (ultrasound) wave frequency is greater than the said acoustical particle resonance frequency.

13. The composition of claim 1 wherein there are multiple acoustic sources.

14. The composition of claim 1 and 10 wherein the acoustic wave (e.g., ultrasonic wave, ultrasound wave) is focused to a site (volume, area, point, etc).

15. The method of claim 14 wherein the acoustic wave is focused from plural different directions.

16. A method to slow, stop, and shrink acoustically active particles suspended in bloodstream by applying acoustic radiation force on the particles, comprising:

    a. Appling acoustic radiation pressure from an acoustic source or sources on acoustically active particle or particles suspended or moving in blood.

    b. Blood, which is contained in any type of vessel flowing at any speed.

    c. Acoustically active particle, or particles, which differ acoustically from the surrounding blood medium, and are suspended inside the blood.

    d. Creating a pushing force on the acoustically active particles by the acoustic radiation pressure. This moves them towards a surface and pushes them against the surface. The speed of the fluid and the particle (if suspended in the fluid) is reduced closer to the surface because of friction and pressure forces, reaching near zero movement at the surface.

    e. The surface is made from any material (biological, and non-biological) and in any shape. The surface can be the wall of the blood vessel or container, and can be put in any direction to the flowing fluid, the acoustically active particles movement direction and the direction in which the acoustic radiation wave advances.

17. The composition of claims 1 and 16, wherein the blood flow is laminar, pulsatile, turbulent, etc.

18. The method of claim 17, wherein the ultrasonic (ultrasound) power is changed according to the blood and particles flowing speed.

19. The composition of claim 16, wherein acoustic pressure is further applied as described in clause V of the detailed description of the invention in order to shrink the bubble.

20. The composition of claim 16, wherein pulsating ultrasonic field is used in order to exert abrupt "whiplash" strikes on the bubbles as they pushed against the surface as described in clause V.b in the Detailed Description of The Invention. The smaller bubbles created dissolve more quickly to the surrounding fluid.

21. The composition of claim 16 wherein a unique ultrasound waveform and cycle regime is applied in order to shrink the gas filled/consist particles faster and more affectively (as described in clause VI in the detailed description of the invention).

22. The composition of claim 1 and 16 wherein the ultrasound waves field (clause I-IV), generated from the acoustic source or sources, can be further focused to a specific volume or point (e.g. site) in the medium in order to increase the acoustic radiation forces in the said site.

23. The composition of claim 1 and 16 wherein the above ultrasound waves field (clause I-IV) is applied in a continuous state, or can be generated on command by human operator or electronic device. The ultrasound waves field can be generated after detection of the acoustically active particles by special ultrasound transducer using the Doppler principle (these transducers available commercially) or any other detection method, depending on use, conditions and need.

24. The composition of claim 1 and 16, wherein the ultrasound waves field intensities, duty cycles, frequencies and acoustic properties and the number of acoustic sources their shape, dimensions placement and acoustic properties, can be fitted and maximized in order to accomplish the best results (of the method) for a given need, use and environment parameters, according to the basic steps (represented by clauses I-IX) set forth in this patent method.

25. The composition of claim 16 wherein the apparatus is the BubbleBuster preferred embodiment, as described in the detailed description of the invention.

26. The composition of claim 1 wherein the apparatus is the BubbleBuster In-line preferred embodiment, as described in the detailed description of the invention.

27. The composition of claim 13 wherein the apparatus is the TheraSite preferred embodiment, as described in the detailed description of the invention.

For the applicant,

Paul Fenster

Fenster & Co. Patent Attorneys, Ltd.

c: 630/02782

Fig 1.1

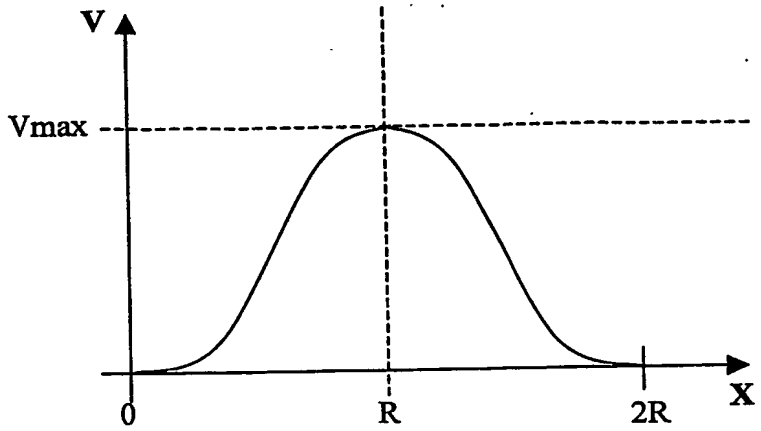


Fig 1.2

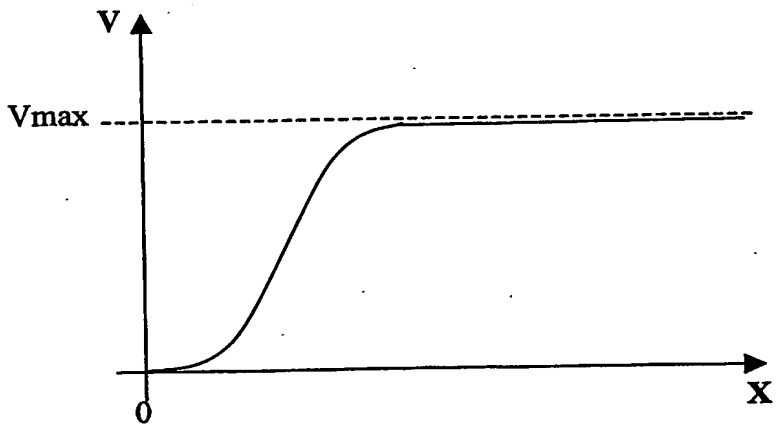


Fig 1.3

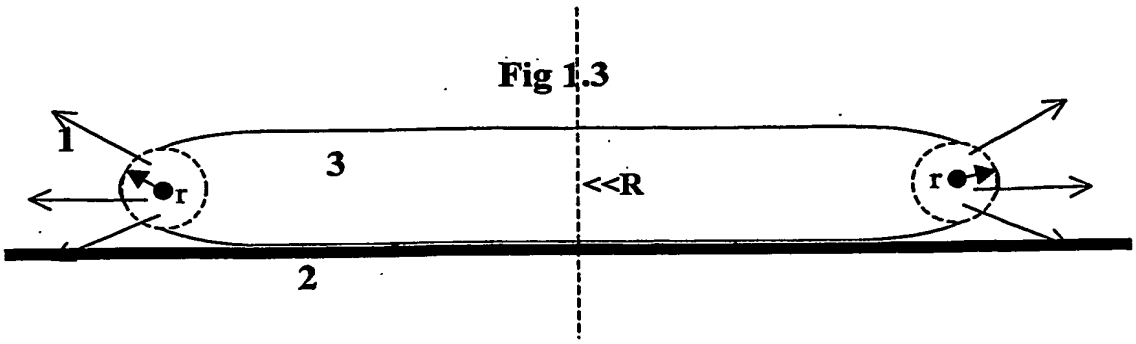


Fig 1.5

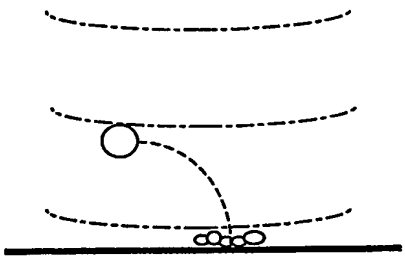


Fig 1.6

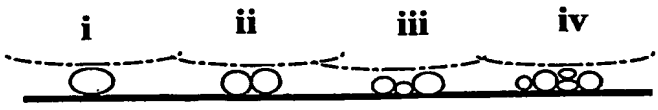
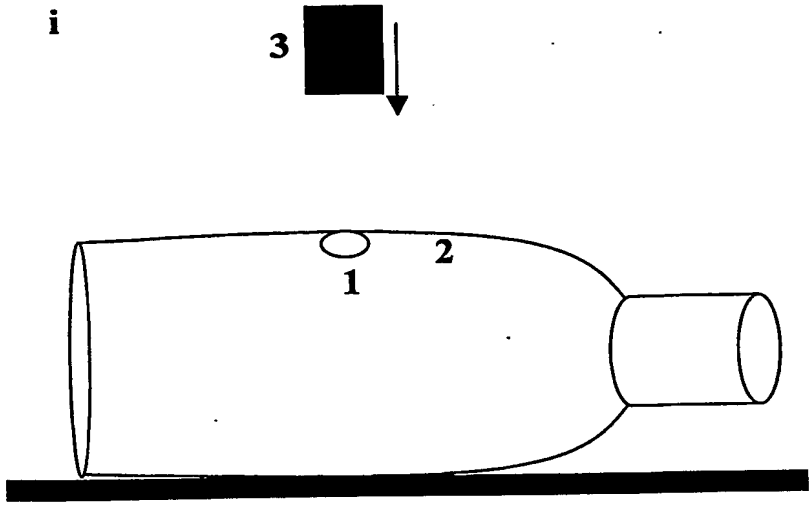


Fig 1.4

i



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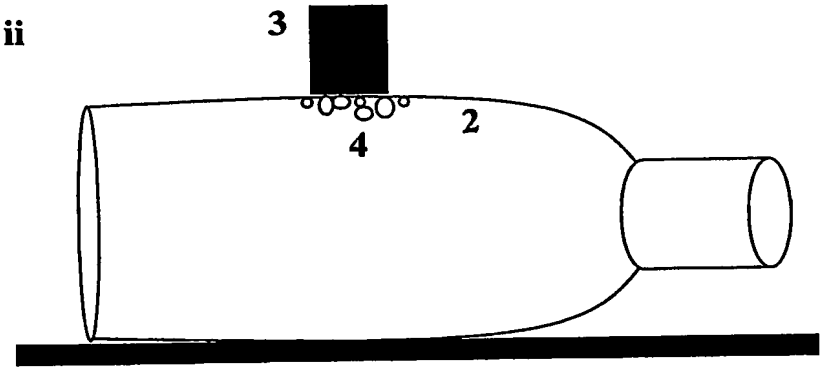


iii

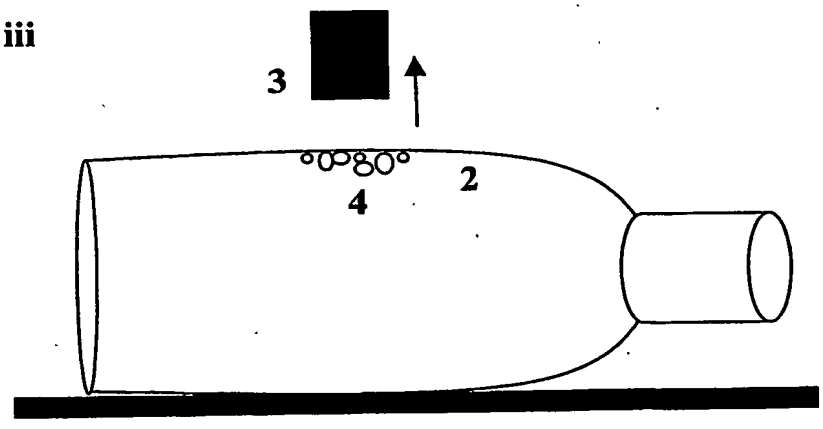


Fig 1.7

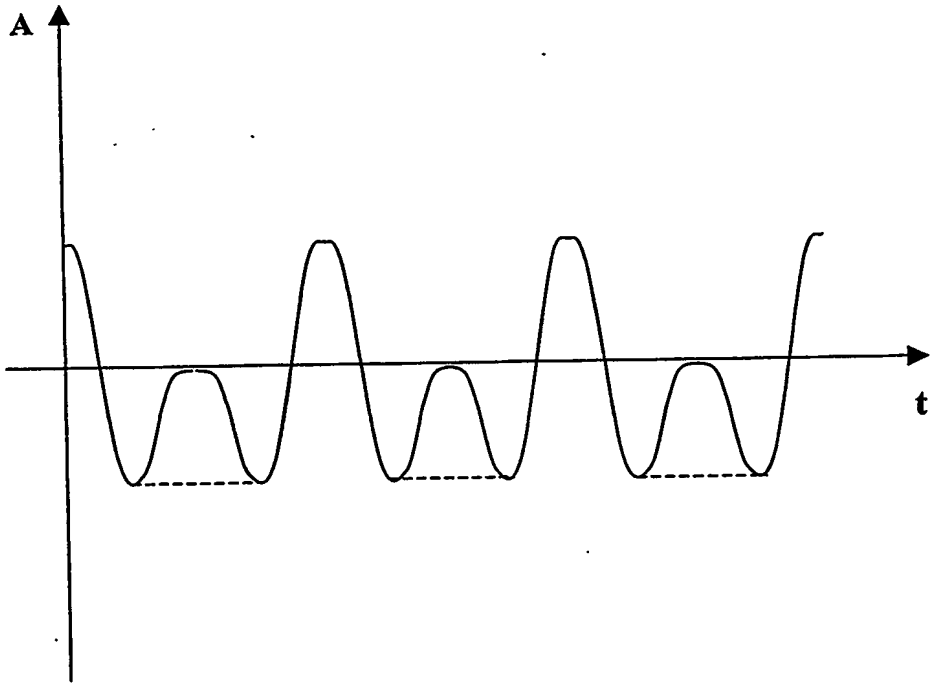


Fig 2.0

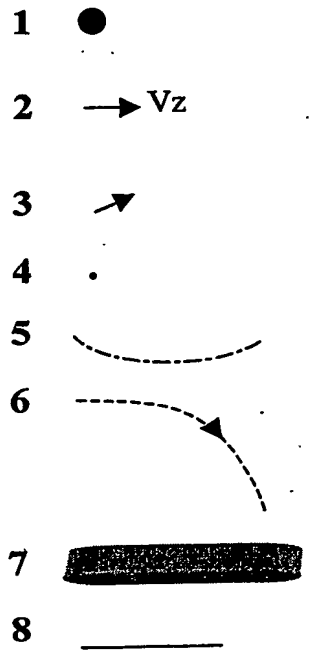


Fig 2.1

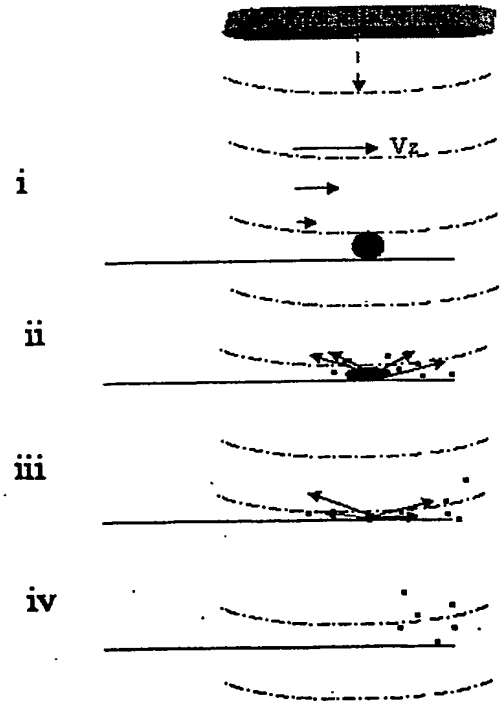


Fig 2.2

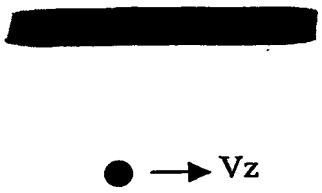


Fig 2.3

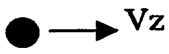


Fig 2.4

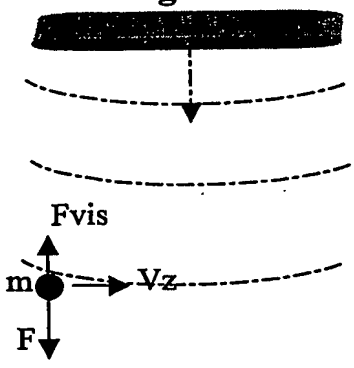


Fig 2.5

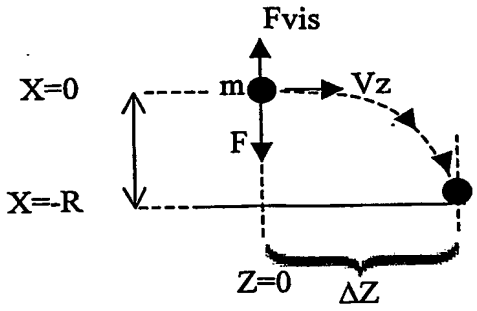
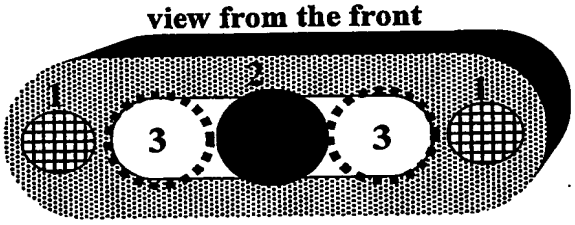


Fig 3.1
Ultrasonic head
view from the front



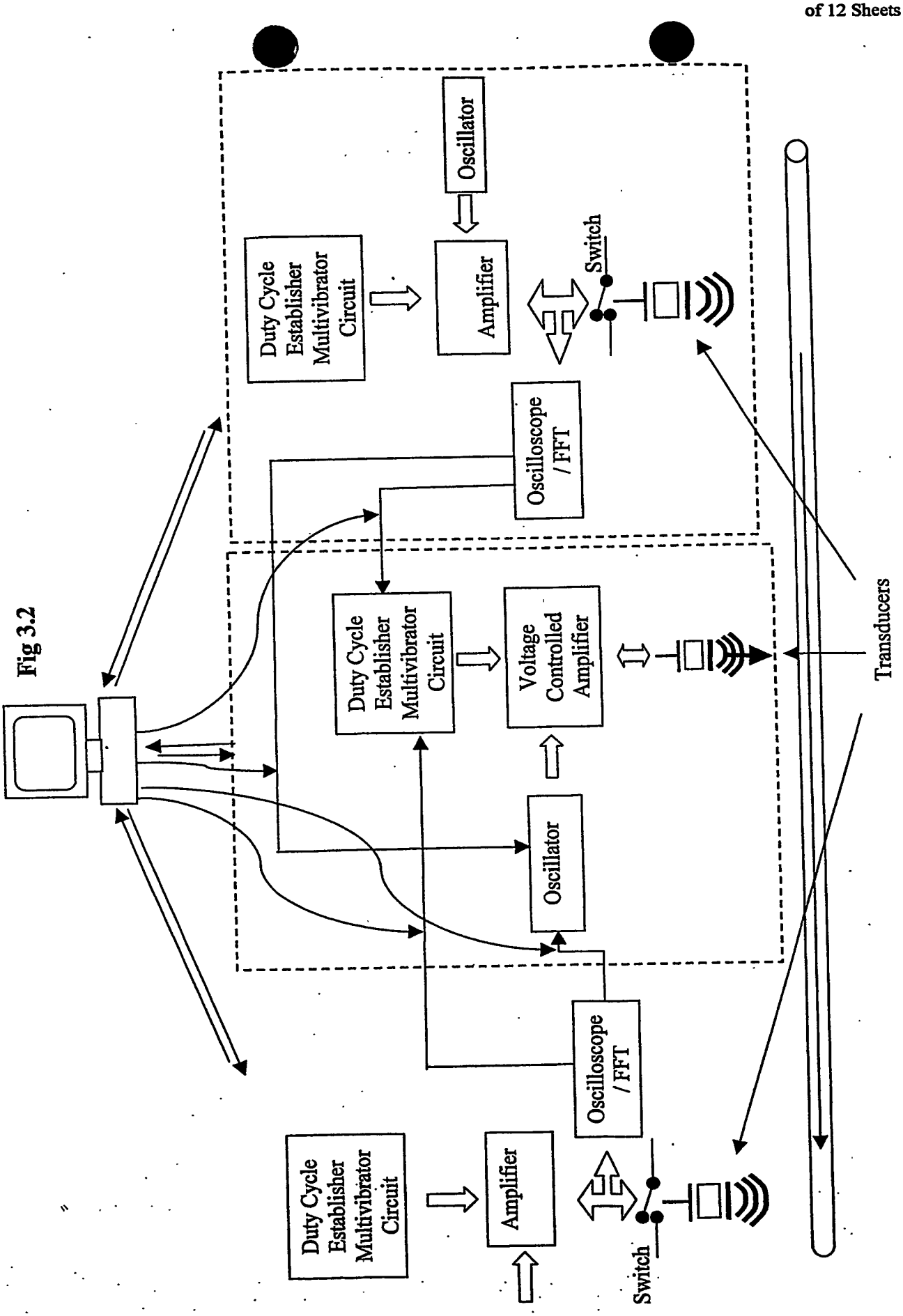

Oscillator
Duty Cycle Establisher Multivibrator Circuit
Amplifier
Switch
Oscilloscope / FFT
Duty Cycle Establisher Multivibrator Circuit
Voltage Controlled Amplifier
Transducers
Oscillator
Oscilloscope / FFT
Duty Cycle Establisher Multivibrator Circuit
Amplifier
Switch

Fig 3.2

Fig 3.3

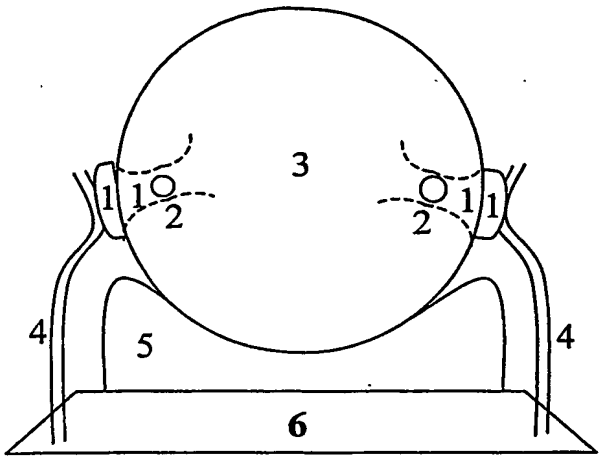


Fig 3.4

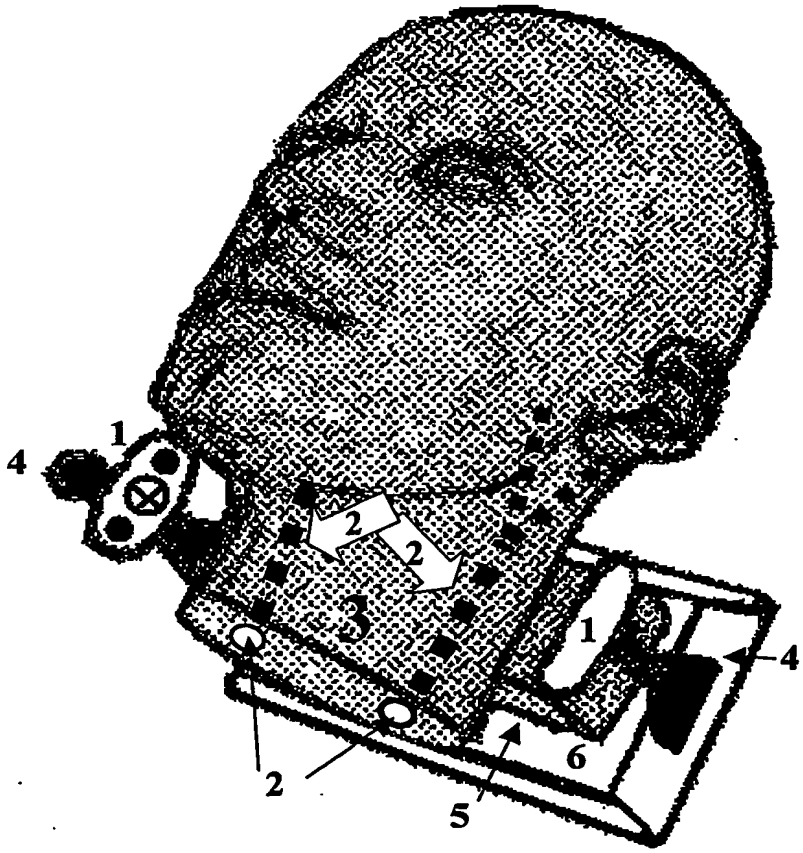


Fig 3.5

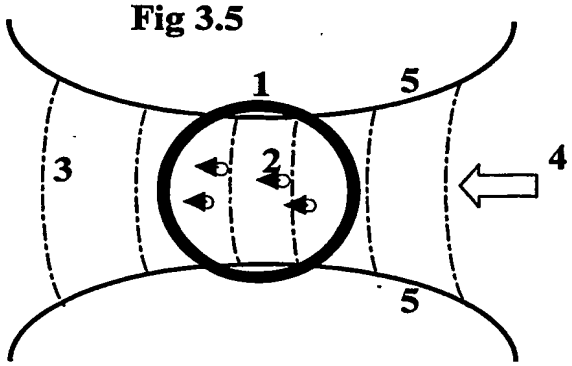


Fig 3.6

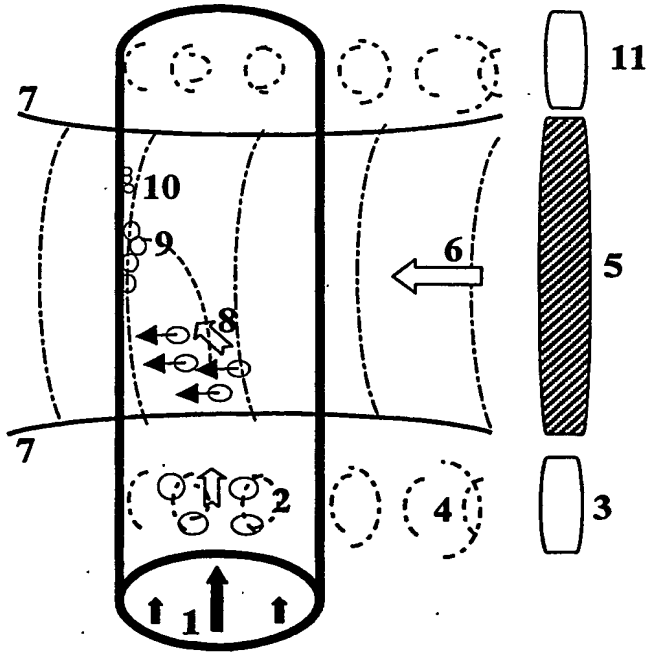


Fig 4.1

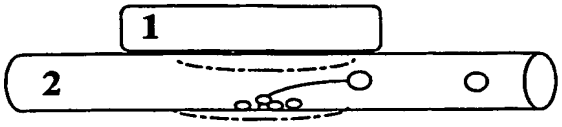


Fig 5.1

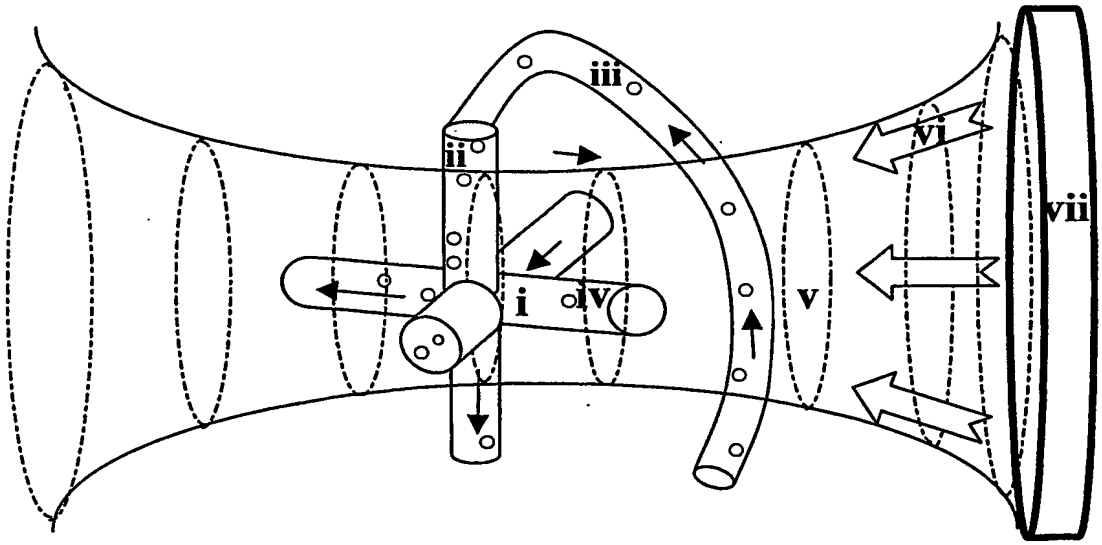


Photo 1

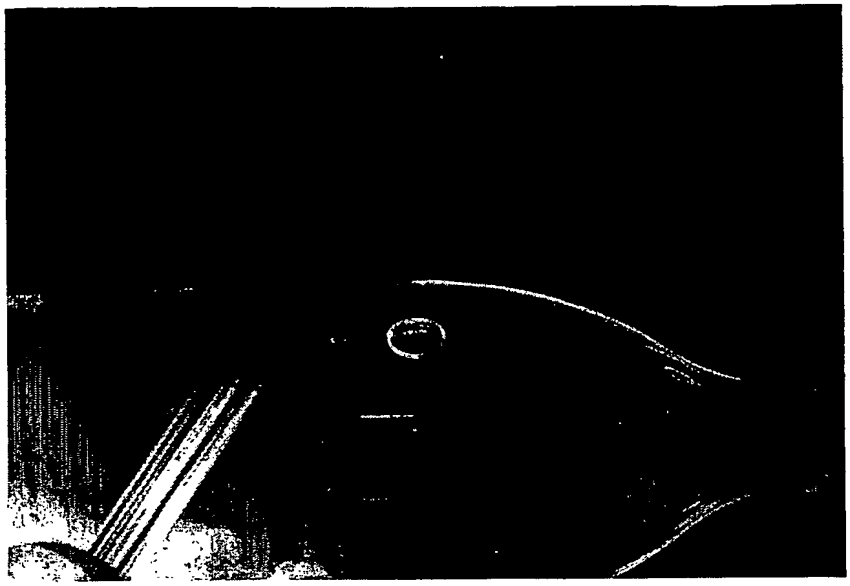
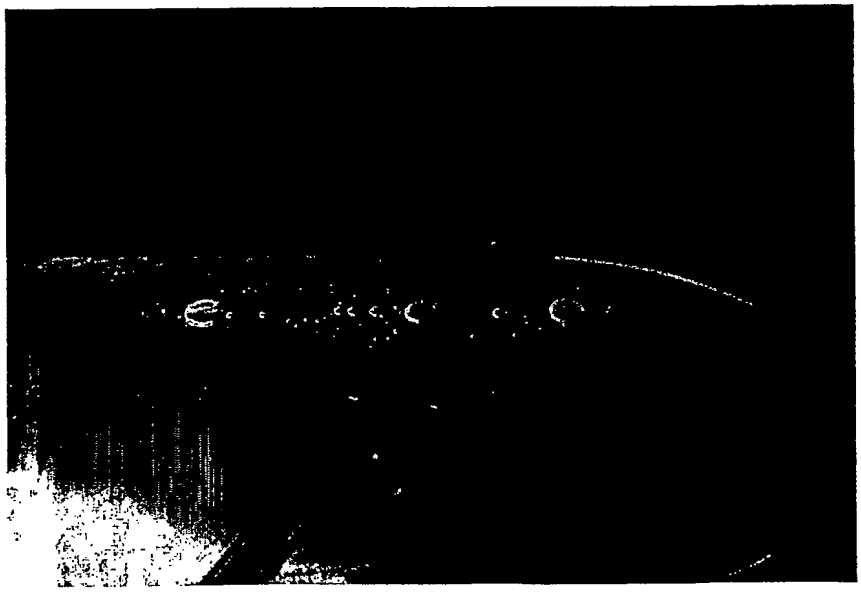


Photo 2



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